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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,320	11/21/2000	Esther H. Chang	2444-109	9632

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EXAMINER
SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
1635	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/716,320	CHANG ET AL.	
	Examin r	Art Unit	
	Mary M. Schmidt	1635	

-- The MAILING DATE f this c mmunication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *9,10,18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,12-17 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 November 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

1. The application claims two lines of priority: first as a CIP of U.S. Application No. 09/480,143 (filed 1/10/00), now abandoned, which is a continuation of U.S. Application No. 08/991,830 (filed 12/16/97), now U.S. Patent 6,0276,892, which claims priority to U.S. Provisional Application 60/034,160 (filed 12/30/96); second as a CIP of U.S. Application No. 09/601,444 (filed 1/4/01), which is a national stage entry of PCT/US98/24657 (filed 11/19/98), which claims priority to U.S. Provisional Applications 60/083,175 (filed 4/27/98) and 60/066,188 (filed 11/19/97).

The corrections to the filing date, inventors, address and title of U.S. Provisional Application 60/066,188 in the fax filed 05/17/02 have been noted and corrected.

Note that priority for the instant claims is given back to U.S. Provisional 60/034,160 (12/30/96) for instant SEQ ID NO:3 and related methods taught in said provisional.

Drawings

2. The drawings have been reviewed by an Official draftsman and a copy of the PTO-948 is attached.

Election/Restriction

3. Applicant's election with traverse of the species RTK (receptor tyrosine kinase) in Paper No. 11, filed 10/24/02, is acknowledged. The traversal is on the ground(s) that "it is clear that the invention has broad applicability to situations in which resistance to radiation or drug treatment is the result of the mutation or overexpression of any of a wide variety of genes." Applicants note that "the invention as disclosed and claimed in this application stems from the fact that cells, such as various tumor cells, can become resistant to radiation therapy or drug treatment. Studies have indicated that radiation resistant phenotype appears to be linked to the activation of specific proto-oncogenes in a signal transduction pathway. The inventors have developed a method of disrupting the pathway to effect a reversal of this drug and resistance phenotype and increase the sensitivity of resistant cells to drug/radiation therapy. The method they have developed involves the administration of an antisense oligonucleotide to modulate the expression of specific proto-oncogenes in the signal transduction pathway which lead to the radiation resistant phenotype. More specifically, the method employs the administration of antisense oligonucleotides complementary to unique sequences of HER-2 genes such that the expression of this factor is reduced. The invention thus provides antisense oligos for reverting radiation and drug resistant cells both *in vitro* and *in vivo* for use in diagnostic assays for detecting the expression of genes in the signal transduction pathway, as listed in claims 8 and 17, which leads to radiation and/or drug resistance and for use as therapeutic agents for inhibiting

tumor cell growth to improve the response to conventional therapeutic agents, thereby improving survival."

This is not found persuasive because claims 8 and 17 are not diagnostic methods for determining whether or not the antisense to HER-2 will have an effect on the claimed gene expression in the drug resistance signal transduction pathways, but are rather methods of treatment of persons having diseases wherein the person is resistant to radiation or drug treatment of said disease, and wherein the drug resistance is due to the mutation or overexpression of the recited genes. Since the claims are drawn to methods of treatment, diseases associated with each one of the claimed genes must be individually searched and considered for treatment with the HER-2 antisense oligonucleotide(s). Since each gene mutation or overexpression could be considered to render the claimed treatments as separate inventions (treatment of different diseases), and since the search for each gene target was considered a burden due to large number of target genes having effects in many different signal transduction pathways, the election of species was required.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 9, 10, 18 and 19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11, filed 10/24/02.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,027,892. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

It would have been *prima facie* obvious to one of ordinary skill in the art to make the composition nucleic acid of instant SEQ ID NO:3 (instant claims 1 and 2) since claim 4 of '892 discloses use of the same composition. It would have been *prima facie* obvious to one of ordinary skill in the art to use an antisense to HER-2 in cells *in vitro* for the function of reducing radiation or drug resistance of the cell (instant claims 3-6) since claims 1-4 of '892 were likewise drawn to methods of reducing radiation or drug resistance of a cell *in vitro* comprising administration an antisense complementary to HER-2 in an amount effective to reduce said radiation or drug resistance; wherein said cell is a carcinoma cell selected from the group consisting of breast, bladder, prostate, head, neck, lung, colon, pancreas, cervical, ovarian, and stomach carcinoma cells; wherein said antisense nucleic acid is introduced by association with a liposome, wherein said antisense nucleic acid comprises SEQ ID NO:3.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 1 and 2 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 1 is drawn to "a therapeutic agent for treating diseases associated with an increase in radiation resistance or drug resistance of a cell, said agent comprising 5'-

TCCATGGTGCTCACT-3' (SEQ ID NO:3) wherein said agent reduces radiation resistance or drug resistance of said cell." Since the claim does not specify that the sequence is isolated, the sequence could read on a sequence comprising the sequence of 5'-TCCATGGTGCTCACT-3' (SEQ ID NO:3) inside a naturally occurring cell. As such the claim embodies non-statutory subject matter.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 3-5, 7, 8, 12-14, 16 and 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 3-5, 7, 8, 12-14, 16 and 17 are drawn to a methods of reducing radiation or drug resistance in cells that either overexpress HER-2 or do not overexpress HER-2 and/or treatment of persons with a disease wherein the person is resistant to radiation or drug treatment of said disease via administering a broad scope of any antisense to any HER-2 gene. Although claims 7,

8, 16 and 17 specify treatment of a person, ie. a human, claims 3-5 and 12-14 specify administration to any cell that embraces cells from any organism.

The specification as filed teaches that SCCHN cell lines JSQ-3, SQ-20B and SCC-61 in vitro were treated with SEQ ID NO:3 and cellular response to radiation was evaluated. See Example 5 on page 22 of the specification. The specification teaches on page 37, lines 22-23, that SEQ ID NO:3 is a 15-mer complementary to a sequence near the initiation codon of the HER-2 gene (Pirollo et al., 1997). On page 40 of the specification, it was taught that female athymic (Ncr nu/nu) mice carrying MDA-MB-435 mammary fat pad xenograft tumors were intravenously injected, via the tail vein, with LipF(B)-AS-HER-2 with docetaxel for dramatic growth inhibition of the tumors (Figure 7). Pages 45-52 further taught experiments in the Ncr nu/nu mice with Tf-LipA-AS-HER-2 (SEQ ID NO:3) with or without radiation, prophetic administration of SEQ ID NO:3 via direct injection to the carcinoma and prophetic treatment of a systemic disease in a patient with SEQ ID NO:3.

MPEP 2163 teaches the following conditions for the analysis of the claimed invention at the time the invention was made in view of the teachings of the specification and level of skill in the art at the time the invention was made:

> The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed

> sequence....A lack of written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process....Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement....The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The specification as filed teaches only one example of an HER-2 antisense, that of SEQ ID NO:3, having an functional correlation to decreasing HER-2 expression in cells *in vitro* and in mice. These teachings do not provide a representative number of species of HER-2 for the claimed functions, reducing radiation or drug resistance in any cell or person. The knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage a representative number of species of HER-2 antisense having the claimed functions from the disclosure of the results with instant SEQ ID NO:3 since functions of antisense in cells in a whole organism were taught in the prior art to be sequence specific (see the references cited below). One of skill in the art would not have recognized that applicant was in possession of a representative number of species of antisense to any HER-2 having the claimed functions because of the lack of teaching in the specification as filed of relevant, specific identifying characteristics of any antisense to HER-2 having the claimed functions.

11. Claims 3-8, 11-17 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the methods claimed in U.S. Patent 6,027,892, and the use of instant SEQ ID NO:3 in carcinoma cells in mice, does not reasonably provide enablement for methods of making and using any HER-2 antisense in any species of organism for the breath of methods claimed for use *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

MPEP 2164 teaches the following standards for a determination of whether the specification taught how to make and use the claimed invention at the time the invention was made by weighing whether or not undue experimentation was required to make and use the invention as claimed. MPEP 2164.01(a) lists the factors for determining "whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) the amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)"

Claims 3-5, 7, 8, 12-14, 16 and 17 are drawn to a methods of reducing radiation or drug resistance in cells that either overexpress HER-2 or do not overexpress HER-2 and/or treatment

of persons with a disease wherein the person is resistant to radiation or drug treatment of said disease via administering a broad scope of any antisense to any HER-2 gene. Although claims 7, 8, 16 and 17 specify treatment of a person, ie. a human, claims 3-5 and 12-14 specify administration to any cell that embraces cells from any organism. Claims 6, 11, 15 and 20 specify that the antisense nucleic acid comprises SEQ ID NO:3.

The specification as filed teaches that SCCHN cell lines JSQ-3, SQ-20B and SCC-61 in vitro were treated with SEQ ID NO:3 and cellular response to radiation was evaluated. See Example 5 on page 22 of the specification. The specification teaches on page 37, lines 22-23, that SEQ ID NO:3 is a 15-mer complementary to a sequence near the initiation codon of the HER-2 gene (Pirollo et al., 1997). On page 40 of the specification, it was taught that female athymic (Ncr nu/nu) mice carrying MDA-MB-435 mammary fat pad xenograft tumors were intravenously injected, via the tail vein, with LipF(B)-AS-HER-2 with docetaxel for dramatic growth inhibition of the tumors (Figure 7). Pages 45-52 further taught experiments in the Ncr nu/nu mice with Tf-LipA-AS-HER-2 (SEQ ID NO:3) with or without radiation, prophetic administration of SEQ ID NO:3 via direct injection to the carcinoma and prophetic treatment of a systemic disease in a patient with SEQ ID NO:3.

There is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation,

and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage using antisense-based technology, ODNs must have certain characteristics. They must be resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetic profile and be nontoxic." Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more

efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. On page 79, col. 2.

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Note also Ma et al. who teach that "*in vitro* subcellular distribution is dependent on the type of ODN modification, cellular system and experimental conditions. ODNs, once internalized, are distributed to a variety of subcellular compartments." (Page 168) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site selection, drug delivery and intracellular localization of the antisense agent." (Abstract) Bennett et al. further taught that "although the antisense paradigm holds great promise, the field is still in its early stages, and there are a number of key questions that need to be answered and technical hurdles that must be overcome....The key issues concerning this class of chemicals center on

whether these compounds have acceptable properties as drugs. These include pharmacokinetic, pharmacological and toxicological properties." (Page 13) As argued above, these issues remain unpredictable in the art for antisense oligonucleotide administration *in vivo*.

Furthermore, in regards to the claimed administration of the antisense *in vivo* using any targeted liposome, there is further a high level of unpredictability for *in vivo* functional administration of the antisense via any type of liposome and any route of administration. As argued above, the antisense must be able to efficiently target the desired target gene location in the desired cell type or tissue type. Fritz et al. and Chirila et al. teach common concerns in the design of suitable delivery vehicles for antisense oligonucleotides but teach the necessarily factors to be considered in the process. For instance Fritz et al. teach on page 272 that "[a]n efficient and versatile drug carrier system has to fulfill the following requirements: (I) particle sizes in the submicrometer range; (ii) the possibility of surface modification; (iii) high drug loading capacity; (iv) colloidal stability of the latex in biological media; and (v) the lack of toxic side effects induced by the carrier or additives." Chirila et al. teach on mechanism of antisense action *in vivo* and the necessary requirement that the antisense be able to internalize into the desired cell target (see page 325). They teach on page 327 that "[e]ncapsulation or incorporation in liposomes is currently the preferred method for the delivery of AS ODNs... and, besides the intravenous infusion and subcutaneous, intramuscular or intraocular injection of naked ODNs, probably the only other method used in human clinical trials. (Ultimately, the suspensions of liposomes are also administered by infusion or injection.)." They also teach that the "*in vivo*

delivery techniques chiefly used at the present, i.e. infusion or injection of naked molecules and liposomal systems, do not assure adequately long-term maintenance of ODNs in tissues."

Although the specification as filed teaches that instant SEQ ID NO:3 may be administered to mice via the exemplified liposomes for certain types of cancer, without further guidance in the specification as filed for mechanisms for administration of any antisense to particular locations in the desired subject, one skilled in the art would necessary practice "trial and error" experimentation to design and implement successful regimens for administration of any other antisense, in any liposome, for the treatment of any type of cancer as broadly claimed.

Finally, although the specification as filed provides by way of example, administration of one antisense (SEQ ID NO:3) to Ncr nu/nu mice, these experiments do not correlate to a teaching of how to make and use the breath of claimed antisense for the breath of methods claimed. As argued above, each antisense must be considered on an antisense-by-antisense basis for use *in vivo* due to the high level of unpredictability for the factors taught above. Additionally, administration of an antisense to a mouse does not provide a teaching of how to make and use the same antisense in other mammals, such as human, unless there is a direct teaching of an expectation of success for the demonstrated physiological effects in both the mouse and in a human. The instant specification as filed does not provide a teaching of how instant SEQ ID NO:3 may be useful in any other mammal for the demonstrated physiological effects *in vivo*. It was known in the art that mouse models are not necessarily predictive of results in humans. Note Sigmund et al. who taught the problems in transgene, knock-out and gene-targeted models.

Since the goal of antisense technology is to down-regulate a specific gene, the use of the mouse for antisense studies of diseases raises analogous issues to those raised by Sigmund and others. Sigmund states in the first para. That "it should not come as a surprise that many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied. Genetic background is the collection of all genes present in an organism that influences a trait or traits. These genes may be part of the same biochemical or signaling pathway or of an opposing pathway or may appear unrelated to the gene being studied. Although all mouse strains contain the same collection of genes, it is allelic variation (sequence differences) and the interactions between allelic variants that influence a particular phenotype. These "epigenic" effects can dramatically alter the observed phenotype and therefore can influence or alter the conclusions drawn from experiments." These effects are relevant to the use of mice to study the use of the instantly claimed antisense for the instantly claimed methods of treatment, since they are problematic barriers in many types of murine models used.

Other problems with use of murine models for the study of antisense effects on disease are found when there is no one murine model indicative of a particular type of disease in other mammals such as human. Note the teachings of Blackshear et al. on the problems of using rodent models for the study of mammary gland carcinogenesis. She taught on pages 105-106 that "[a]nimal models of spontaneous and chemically induced mammary gland carcinogenesis have provided some insight into the pathogenesis of breast cancer but do not faithfully mimic the pathology or biological behavior of human breast cancer.... there is no single model that best

mimics the pathology and mechanistic deregulation seen in breast cancer. Each model provides a small portion of the puzzle, which helps to clarify the complex interactions associated with the heterogeneous population of cells in the normal mammary gland. These models enable the researcher to examine individual or combinations of perturbations that lead to the initiation and progression of breast cancer." Thus, absent use of an art recognized mouse model of human disease, the art teaches a high level of unpredictability for the correlation of specific treatment results in mice with an expectation of success of the equivalent effects in humans.

One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecules *in vivo* (other than instant SEQ ID NO:3 in mice) and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

12. The claims are free of the prior art since the prior art does not teach nor fairly suggest HER-2 antisense oligonucleotides.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to *Katrina Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt
December 28, 2002